

instruments – the ultracentrifuge and electron microscope – and the associated techniques that enabled scientists to gain unprecedented access to the mechanisms of the cell. I discuss the ultracentrifuge in Section 2 and the electron microscope in Section 3.

2. THE ULTRACENTRIFUGE AND CELL FRACTIONATION

As discussed in Chapter 2, to understand a mechanism scientists try to decompose it into its component parts (structural decomposition) and operations (functional decomposition). Perhaps the most obvious strategy is to isolate certain parts and see what each does. In cells, for example, simply learning what chemical compounds are typically found in each component part may be informative as to what role each part plays in the cell's functioning. If a specific enzyme appears in a particular organelle, for example, then it is likely that the reaction catalyzed by that enzyme is localized there. The critical first step is to isolate the component parts and operations and the challenge is to do so in a way that divides components as they are in the natural system. This is extremely challenging. The living cell is a highly structured milieu in which components are integrated structurally and functionally.

How then to decompose cells into their component parts? Two candidates seemed to be available – mechanical forces and chemical processes. Centrifugal force as generated in a centrifuge, which can separate particles by size and weight, was a promising mechanical candidate. However, it required some means of breaking cell membranes so as to access the contents and combine the contents of multiple cells into one container. One plausible way of breaking cell membranes was to apply chemical agents that would dissolve them. Accordingly, in 1869 the Swiss biologist, Johann Friedrich Miescher, employed first warm alcohol and then the enzyme pepsin to strip away both the cell membrane and the cytoplasm of the cell in an attempt to isolate cell nuclei. He subjected the remaining material to centrifugation to isolate the nucleus from the debris, and then subjected the nucleus itself to chemical analysis. In this manner, Miescher (1871) identified a new group of cellular substances which he named *nucleins*; when his student Richard Altmann (1889) identified them as acids, he renamed them *nucleic acids*.

Although various researchers in the early twentieth century, including Otto Warburg, employed centrifugation in attempts to isolate cell structures, the technique did not come into wide use at the time. There are a couple of reasons for this. First, many researchers were skeptical of techniques that disrupted the internal structure of the cell, which they assumed was critical